1. P DRUG PRODUCT (Ferric Hydroxide Polymaltose Complex / UNI­

PHARMA Chw. tablets 100 mg/tab)

1. ***P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT***

***(Ferric Hydroxide Polymaltose Complex / UNI-PHARMA Chw. tablets 100 mg/tab)***

1. ***P.1.1 Description of The Drug Product***

The drug product is presented as brown/white, mosaic, cylindrical tablets of 12.0 ± 2 mm diameter, packaged in ALU/ALU blisters, so that the product is completely shielded from the environmental conditions, especially from humidity.

***2.3. P.1.2 Composition of The Drug Product***

|  |  |
| --- | --- |
| **Quantity where the composition refers to** | **730.000** |
| **Unit of measurement** | **mg** |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **No** | **Name of ingredient(s)** | **Reference to standards** | **Quantity (mg/tab)** | **Function** |
| ***Active ingredient(s):*** | |  | | |
| 1. | Ferric Hydroxide Polymaltose Complex | I.H.S. | 357.000 | Active ingredient |
| Corresponds to Iron+++ | 100.000 |
| ***Other ingredient(s):*** | |  | | |
| 1. | Sodium Cyclamate | Current Eur.  Pharm. | 9.000 | Sweetener |
| 2. | Vanillin | Current Eur.  Pharm. | 2.900 | Aroma |
| 3. | Polyethylene Glycol 6000 | Current Eur.  Pharm. | 37.000 | Binder |
| 4. | Chocolate Flavor | I.H.S. | 0.600 | Flavoring agent |
| 5. | Dextrates (Emdex) | Current USP. | 261.000 | Diluent, binder. |
| 6. | Talc | Current Eur.  Pharm. | 21.000 | Lubricant |
| 7. | Cellulose Microcrystalline | Current Eur.  Pharm. | q.s. 730.000 | Diluent |
| 8. | Water Purified \* | Current Eur.  Pharm. | - | Solvent |

\*Solvent that is evaporated during production

***DETAILS OF ANY OVERAGES:***

- Active substance(s): Not Applicable

- Excipient(s): Not Applicable

1. ***P.2 PHARMACEUTICAL DEVELOPMENT***

The pharmaceutical product **Ferric Hydroxide Polymaltose Complex / UNI-PHARMA *Chw. tablets 100 mg/tab*** contains Iron Hydroxide Polymaltose, indicated for the treatment of Iron deficiency anemia.

Stability studies of the selected, optimized formula, at normal and accelerated conditions have been performed in order to validate that it remains stable throughout the shelf life of the product.

After production of trial batches and performance of the required controls, the formula described in section *3.2.P.1.2* was chosen as optimal.

The Pharmaceutical Development section describes the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. Those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality are determined.

The present formulation is supplied in chewable tablets. Each tablet weighs 730 mg.

Packaging, nature, type and qualitative composition of the container materials are all of excellent quality, within the demanded standards and capable of been used for food and drugs preparations.

1. ***P.2.1 Components Of The Drug Product***

The product **Ferric Hydroxide Polymaltose Complex / UNI-PHARMA *Chw. tablets 100 mg/tab*** consists of the following active pharmaceutical ingredient:

• *Ferric Hydroxide Polymaltose Complex* by Global Calcium Ltd

The excipients used are described in further detail below.

1. ***P.2.1.1 Drug Substance***

*Active substance:*

**FERIC HYDROXIDE POLYMALTOSE COMPLEX / GLOBAL CALCIUM**

PRIVATE LIMITED

**INN:** Ferric Hydroxide Polymaltose Complex

**Chemical name:** (S)-2- amino-3-[4-(4-hydroxy-3,5-di-iodophenoxy)-3,5-di-iodophenyl]

propanoate

**CAS No:** 53858-86-9

**Compendial names:** Not Available

**Other names:** Polymaltosate iron (III)

Iron polymaltose

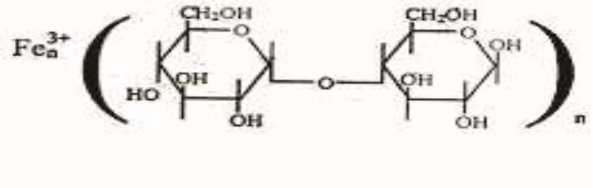
Ferric polymaltose

Iron (III)-hydroxide polymaltose complex

**Structural Formula**

The structural formula of Ferric Hydroxide Polymaltose Complex is not determined.

A general structural formula of Ferric Hydroxide Polymaltose Complex is presented below.



Molecular Formula

The empirical formula of this high molecular weight complex of iron (III)-hydroxide and polymaltose can be expressed as follows: [Fe(OH)3 x (H2O)1,5]n x [C6H10O5)m]x where:

n number of mono-hemi-hydrated iron(III)-hydroxide complexes (iron polymerization rate)

m polymerization rate of the anhydrous-dextrose ligand (polymaltose/polymerized-maltose complex)

x stoichiometric factor (correlation factor between the content of iron(III)-hydroxide and of polymaltose ligand)

Molecular Weight

The relative molecular weight is between 100000Da and 350000Da approximately.

Iron Polymaltose Complex is a polysaccharide-iron complex, which is a novel iron preparation used in the treatment of iron deficiency anemia. Iron, an essential constituent of the body, is necessary for haemoglobin formation and for the oxidative process of living tissue. **Ferric Hydroxide Polymaltose Complex / UNI-PHARMA *Chw. tablets 100 mg/tab*** contains non-ionic Ferric Iron and Polymaltose in a stable complex. This facilitates a controlled absorption of the Ferric Iron when it comes in contact with the mucosal cell surface. Being non-ionic, it does not release any free radicals; thus no toxic effects are presented due to the release of free radicals as noticed with the traditional ionized iron salt preparations. It does not interact with the food components and other medications; thus, unlike ferrous salts, there is no decrease in bioavailability of Iron Polymaltose Complex. This ensures that with the consumption of this complex, Iron gets utilized at a faster rate in the haemoglobin and myoglobin synthesis.

1. ***Appearance, Color, Odor, Taste***

Ferric Hydroxide Polymaltose Complex is presented as a brown or deep brown coloured, free flowing and amorphous powder. It is practically odorless, with strong metallic taste.

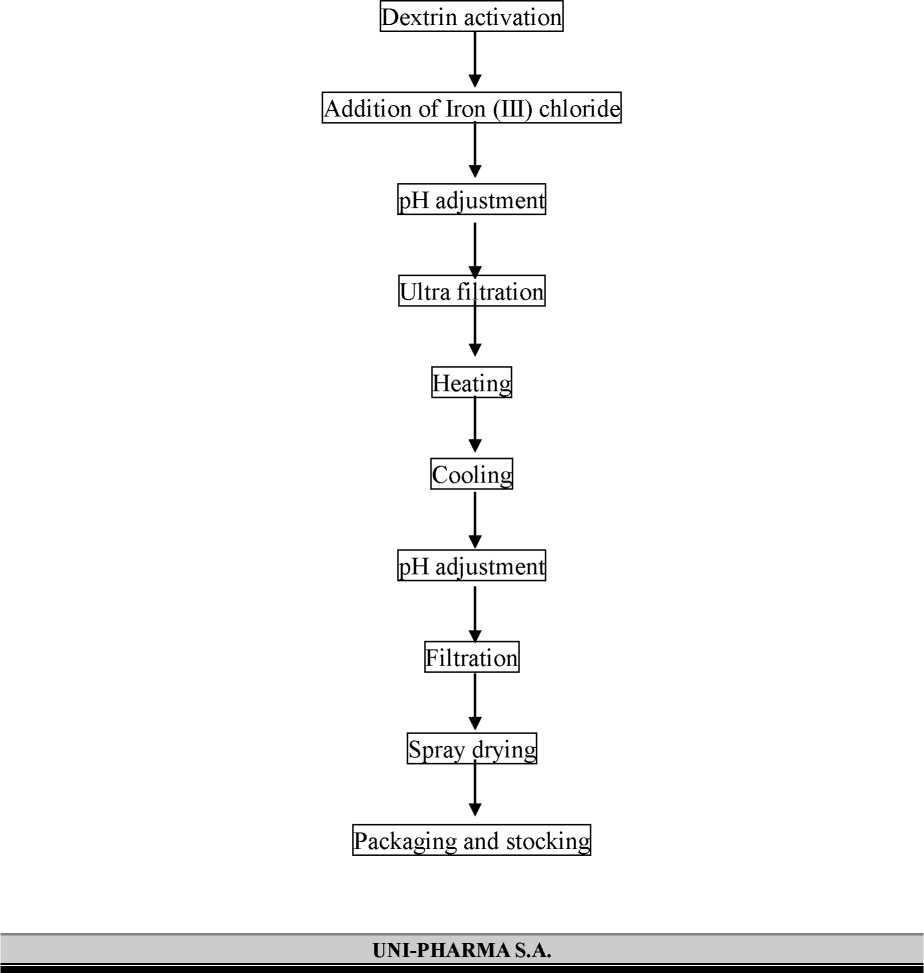
1. ***Physical Properties***

Iron Polymaltose is a water soluble, macro-molecular complex of Iron (III) hydroxide and isomaltose. It is soluble in water but insoluble in organic solvents. pH of a 5% w/v aqueous solution of Iron (III) stays between 5.5 and 7.5.

The product is manufactured by **GLOBAL CALCIUM PRIVATE LIMITED**

1. ***Synthetic Routes***

**Flow chart of the synthetic process**



1. ***Impurities***

**Potential impurities originating from the route of synthesis**

The potential impurities coming from the synthesis method, together with their acceptance limits, are the following:

* Sodium chloride: < 3.0% on dry basis

Heavy metals:

* Arsenic: < 2.0 ppm
* Copper: < 60 ppm
* Lead: < 20 ppm
* Zinc: < 150 ppm

Potential impurities from degradation and detected by exposing the drug substance to critical environmental conditions

The degradation of the iron (III)-hydroxide polymaltose complex can cause the uncomplexation of the two components, i.e. polymerized iron (III)-hydroxide and polymaltose (polymerized dextrin).

The possible occurrence of free iron(III) is revealed by the formation of a precipitate or by some turbidity in the solution.

The free iron(III) is controlled at the release of the drug substance as well as during all stability period and it should be < 0.05%.

Residual Solvents

Only water is employed for the manufacturing process, so there is no potential for residual solvent to be present in the final product.

The moisture limit for the final API is < 8.0%.

For further information, please refer to the ASMF of the manufacturers.

1. ***Stability***

Each sample for stability studies is stored in double polyethylene bags each closed with a plastic band; these bags are carefully closed and preserved into suitable containers. This sort of packaging simulates the condition of the final bulk package that exits from the production line.

Normal test conditions:

Each of the samples is stored under long-term conditions of 25 ± 2 °C and 60 ± 5% humidity conditions according to ICH guidelines.

After the initial analysis, the samples are analyzed at intervals of 3, 6, 9, 12, 18, 24, 36, 48 and 60 months.

The following analytical controls are performed:

* Characteristics

Specifications: brown or dark red, odorless powder

* Appearance of 5% w/v Fe3+ solution

Specifications: clear and free from undissolved matter

* pH 5% w/v aqueous solution Fe3+

Specifications: 5.50 - 7.50

* Loss on drying

Specifications: < 8.0%

* Assay Iron (III) o.d.b.

Specifications: 26.0%-36.0%

* Assay Polymaltose o.d.b.

Specifications: 25.0%-50.0%

* Free Iron (III)

Specifications: < 0.05%

* Total bacterial charge

Specifications: < 1000 CFU/g

* Moulds/Yeasts

Specifications: < 100 CFU/g

Accelerated test conditions:

Each of the samples is stored at 40 ± 2 °C and 75 ± 5% humidity conditions.

After the initial analysis, the samples are analyzed at 1, 3 and 6 months according to ICH Guidelines.

The following analytical controls are performed:

* Characteristics

Specifications: brown or dark red, odorless powder

* Appearance of 5% w/v Fe3+ solution

Specifications: clear and free from undissolved matter

* pH 5% w/v aqueous solution Fe3+

Specifications: 5.50 - 7.50

* Loss on drying

Specifications: < 8.0%

* Assay Iron (III) o.d.b.

Specifications: 26.0%-36.0%

* Assay Polymaltose o.d.b.

Specifications: 25.0%-50.0%

* Free Iron (III)

Specifications: < 0.05%

* Total bacterial charge

Specifications: < 1000 CFU/g

* Moulds/Yeasts

Specifications: < 100 CFU/g

For further information, please refer to the ASMF of the manufacturers.

1. ***Forced Degradation Studies***

Ferric Hydroxide Polymaltose Complex is an inorganic/organic polymer, consisted out of a Hydroxy-Fe+++ ‘core' and polymaltose. According to the manufacturing process of the raw material, a Hydroxy-Fe+++ ‘core' is being created by the addition of the activated Dextrin along with the addition of FeCl3 and Na2CO3. The pH of the resulting material is adjusted - in order to stabilize it- in a high alkaline value, by adding 10 N NaOH, while on the next manufacturing step the pH value is dropped by the addition of HCl 6N and adjusted to 5.0 in order to achieve condensation and obtain the raw material by ultra-filtration.

Several tests in various stress media and conditions were applied both to the raw material and the finished product.

*Table 3.2.P.2.1.1.1* Indicators of degradation of **Ferric Hydroxide Polymaltose Complex & Ferric Hydroxide Polymaltose Complex / UNI-PHARMA Chw. tablets 100 mg/tab**,

in various stress media and conditions

|  |  |  |  |
| --- | --- | --- | --- |
| **Ferric Hydroxide Polymaltose Complex &**  **Ferric Hydroxide Polymaltose Complex / UNI-PHARMA Chw. tablets 100 mg/tab** | | | |
|  | **Indicators of Degradation** | | |
| **Stress media &**  **Exposure conditions** | **Polymaltose**  **Oxidation** | **Deconstruction/ Uncomplexation of molecule** | **Polymaltose Oxidation (Primary alcohol^Aldehyde^- Acid)** |
| **NaOH 0.1 M** | - | - | - |
| **H2O** | V | - | - |
| **H2O2** | V | - | - |
| **HCl 0.1 M** | - | V | - |
| **Photostability** |  | - | V |

According to the raw material's manufacturing process, both the product and the raw material are considered stable for more than 24 hours when exposed to alkaline environment since this is the primary environment for stabilization of the raw material.

The same applies when both the product and the raw material are exposed into oxidizing environment, water and humidity, since Iron's (III) charge cannot be oxidized any further. Photostability studies in both the product and the raw material showed no signs of degradation either, so both can be considered as photostable.

Exposure of the product and the raw material into acidic environment can cause from partial to full deconstruction of the molecule (due to the Hydroxy- groups that carries) even back to FeCl3 depending on how low the pH value may drop. Both the product and the raw material though are considered stable when the pH value is around 3.0.

1. ***Ionized Iron+++ (Free Iron+++)***

According to the *Table 3.2.P.2.1.1.1,* full or partial uncomplexation of the colloidal molecule of Ferric Hydroxide Polymaltose Complex occurs when it gets exposed to acidic environments and especially when the pH value drops below 1.

At that point, Iron+++ ions are released into the solution which can be detected by the addition of OH- in the resulting solution (pH value raises). Free Iron+++ ions join together with OH- to form Fe(OH)3 which drops down as an intense brown precipitate. Please refer to *§3.2.P.5.2.3.1* for a detailed description of the method applied.

The test for the presence of Ionized Iron+++ was performed to samples of the product and the raw material right after when both were exposed to various stress media and conditions. Since uncomplexation of the molecule of Ferric Hydroxide Polymaltose Complex occurs when it gets exposed to acidic environments, the method for the detection of Ionized Iron+++ was expected to present positive results when the samples were exposed to HCl 0.1M. Results are presented in the tables below.

*Table 3.2.P.2.1.1.2* Samples **of Ferric Hydroxide Polymaltose Complex** exposed to various stress media and tested for presence or absence of Ionized Iron+++.

|  |  |
| --- | --- |
| **Ferric Hydroxide Polymaltose Complex** | |
| **Stress media &**  **Exposure conditions** | **Ionized Fe+++ Test** |
| **NaOH 0.1 M** | (-) Negative |
| **H2O** | (-) Negative |
| **H2O2** | (-) Negative |
| **HCl 0.1 M** | (+) Positive |
| **Photostability** | (-) Negative |

*Table 3.2.P.2.1.1.3* Samples of **Ferric Hydroxide Polymaltose Complex / UNI­PHARMA Chw. tablets 100 mg/tab** exposed to various stress media and tested for presence or absence of Ionized Iron+++.

|  |  |
| --- | --- |
| **Ferric Hydroxide Polymaltose Complex / UNI-PHARMA**  **Chw. tablets 100 mg/tab** | |
| **Stress media &**  **Exposure conditions** | **Ionized Fe+++ Test** |
| **NaOH 0.1 M** | (-) Negative |
| **H2O** | (-) Negative |
| **H2O2** | (-) Negative |
| **HCl 0.1 M** | (+) Positive |
| **Photostability** | (-) Negative |

1. ***Current API Specifications (set by Uni-Pharma S.A. for incoming Ferric***

***Hydroxide Polymaltose Complex)***

|  |  |
| --- | --- |
| **Tests** | **Specifications** |
| **Appearance** | Brown or dark brown, odorless powder |
| **Solubility** | Soluble in water. Practically insoluble in organic solvents |
| **Identification** |  |
| **Combined Iron (III)** | Positive |
| **Polymaltose** | Positive |
| **Appearance of 5% Fe3+ w/v solution** | Clear and free from undissolved matter |
| **Loss on drying** | NMT 8.0% |
| **pH (sol. 5% w/v Fe3+ )** | 5.5-7.5 |
| **Assay Iron (III) - on dry basis** | 26.0% - 36.0% |
| **Assay Polymaltose** | 25.0% - 50.0% |
| **Chlorides (as NaCl, on dry basis)** | NMT 3.0% |
| **Free Iron (III) (sol. 5% w/v Fe3+ )** | NMT 0.05% |
| **Arsenic** | NMT 2 ppm |
| **Copper** | NMT 60 ppm |
| **Lead** | NMT 20 ppm |
| **Zinc** | NMT 150 ppm |
| **Total bacterial count** | NMT 1000 CFU/g |
| **Moulds/Yeasts** | NMT 100 CFU/g |
| **Enterobacteria** | NMT 100 CFU/g |
| ***Escherichia coli*** | Absent on 1 g |
| ***Staphylococcus aureus*** | Absent on 1 g |
| ***Salmonella*** | Absent on 10 g |
| ***Pseudomonas aeruginosa*** | Absent on 1 g |

1. ***P.2.1.2 Excipients***

For the development of this formulation specific excipients have been used, which have been chosen taking into consideration factors as the ones that follow:

* Compatibility with the active substance.
* Adjustment to the conditions and the manufacturing procedure of the specific pharmaceutical form.
* Chemical Inertia.
* Special characteristics concerning each excipient, which contribute to the final product properties.

The excipients used are summarized as follows:

|  |  |
| --- | --- |
| **Polyethylene Glycol 6000** | Binder in kneading process |
| **Cellulose Microcrystalline** | Diluent |
| **Dextrates** | Diluent, binder. |
| **Talc Purified** | Lubricant |
| **Sodium Cyclamate** | Sweetener |
| **Vanillin** | Aroma |
| **White Chocolate Flavor** | Flavoring agent |

All of the above excipients (apart from Dextrates, described in the current USP-NF) are described in Eur. Pharmacopoeia monographs and they are of the appropriate compendial quality. The excipients are tested for microbial bioburden in compliance with the Eur. Pharmacopoeia method.

All the used excipients are common and inert, they lack toxicity and are widely used in pharmaceutical preparations.

The flavouring agent used, is tested according to the manufacturer's in-house specifications.

**Excipients Described in a Pharmacopoeia:**

* Sodium Cyclamate

Sodium Cyclamate is the [sodium](http://en.wikipedia.org/wiki/Sodium) [salt](http://en.wikipedia.org/wiki/Salt) of [cyclamic acid](http://en.wikipedia.org/wiki/Cyclamic_acid) (Cyclohexanesulfamic acid), which itself is prepared by the [sulfonation](http://en.wikipedia.org/wiki/Sulfonation) of [cyclohexylamine.](http://en.wikipedia.org/wiki/Cyclohexylamine) This can be accomplished by reacting cyclohexylamine with either [sulfamic acid](http://en.wikipedia.org/wiki/Sulfamic_acid) or [sulfur trioxide.](http://en.wikipedia.org/wiki/Sulfur_trioxide) Sodium cyclamate is an [artificial sweetener.](http://en.wikipedia.org/wiki/Artificial_sweetener) It is often used synergistically with other artificial sweeteners, especially [saccharin;](http://en.wikipedia.org/wiki/Saccharin) the mixture of 10 parts cyclamate to 1 part saccharin is common and masks the off-tastes of both sweeteners.

* Polyethylene Glycol (Macrogol) 6000

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations.

Solid grades (PEG >1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor.

Grades of PEG 6000 and above are available as free-flowing milled powders.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating.

* Cellulose Microcrystalline

Microcrystalline Cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct- compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a nontoxic and nonirritant material. Microcrystalline Cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

* Dextrates

The USP35-NF30 describes dextrates as a purified mixture of saccharides resulting from the controlled enzymatic hydrolysis of starch. It may be either hydrated or anhydrous. Its dextrose equivalent is not less than 93.0% and not more than 99.0%, calculated on the dried basis.

Dextrates is a directly compressible tablet diluent used in chewable, non-chewable, soluble, dispersible, and effervescent tablets. Dextrates may also be used as a binding agent by the addition of water, no further binder being required. Tablets made from dextrates increase in crushing strength in the first few hours after manufacture, but no further increase occurs on storage.

Dextrates is a purified mixture of saccharides resulting from the controlled enzymatic hydrolysis of starch. It is either anhydrous or hydrated. In addition to dextrose, dextrates contains 3-5% w/w maltose and higher polysaccharides.

Dextrates comprises white spray-crystallized free-flowing porous spheres. It is odorless with a sweet taste (about half as sweet as sucrose).

Dextrates is used in oral pharmaceutical formulations and is generally regarded as a relatively nontoxic and nonirritant material

* Talc

Talc is widely used in oral solid dosage formulations as a lubricant and diluent. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent. Various grades of talc are commercially available that vary in their chemical composition depending upon their source and method of preparation.

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material.

* Vanillin

Vanillin is a white or cream, crystalline needles or powder with characteristic vanilla odor and sweet taste.

Vanillin is widely used as a flavor in pharmaceuticals, foods, beverages, and confectionery products, to which it imparts a characteristic taste and odor of natural vanilla. It is also used in perfumes, as an analytical reagent and as an intermediate in the synthesis of a number of pharmaceuticals, particularly methyldopa.

Additionally, it has been investigated as a potential therapeutic agent in sickle cell anemia and is claimed to have some antifungal properties.

In food applications, vanillin has been investigated as a preservative. As a pharmaceutical excipient, vanillin is used in tablets, solutions (0.01-0.02% w/v), syrups, and powders to mask the unpleasant taste and odor characteristics of certain formulations. It is similarly used in film coatings to mask the taste and odor of vitamin tablets.

* Water, Purified

Water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorized.

Purified water in bulk is prepared by distillation, by ion exchange, by reverse osmosis or by any other suitable method from water that complies with the regulations on water intended for human consumption laid down by the competent authority.

Purified water in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination. In order to ensure the appropriate quality of the water, validated procedures and in-process-monitoring of the electrical conductivity and regular microbial monitoring are applied.

Purified water in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination. During production and subsequent storage, appropriate measures are taken to ensure that the microbial count is adequately controlled and monitored.

Excipient(s) Not Described in a Pharmacopoeia:

• White Chocolate Flavor

Flavoring agent.

1. ***P.2.2 Drug Product***

“Ferric Hydroxide Polymaltose Complex / UNI-PHARMA *Chw. tablets 100 mg/tab”*

The product is presented as chewable tablets of Ferric Hydroxide Polymaltose that corresponds to 100 mg/tab Iron3+, packaged in an ALU/ALU blister.

Excipients for Uni-Pharma's formulation were chosen carefully to give appropriate dissolution rate and stability of the finished dosage form, with ultimate goal to develop a stable immediate release formulation, matching the reference product, both in vivo and in vitro.

Manufacturing process for tablets should meet the requirements of Good Manufacturing Practice (GMP).

Throughout manufacturing certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production.

The validation of the manufacturing process and the in-process controls are documented.

1. ***P.2.2.1 Formulation Development***

Chewable tablets are formulated and manufactured so that they may be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste. These tablets have been used in tablet formulations for children, especially multivitamin formulations, and for the administration of antacids and selected antibiotics. Chewable tablet formulations, particularly those containing pharmaceutically active agents, present issues of organoleptic characteristics of odor, taste, appearance and mouth feel. The formula ingredients and manufacturing process both play a role in obtaining the desired organoleptic properties. Additionally, chewable tablets facilitate more rapid release and hence more rapid absorption of active ingredients and provide quick onset of action.

Manufacturing of tablet products is generally done using either a wet granulation process or direct compression. The wet granulation process typically involves wet massing of the formula ingredients using a liquid to form aggregates. The process requires a drying step to remove the liquid, following which the dried aggregates are reduced to an appropriate size by milling. Over-wetting of granules in the wet granulation process can produce harder granules. Tablets made from such granulations often have a gritty mouth-feel when chewed. This grittiness can be avoided by using a direct compression manufacturing process which eliminates the wet massing and subsequent drying steps.

Most compressed tablets consist of the active ingredient and a diluent (filler), binder, disintegrating agent, and lubricant. Approved dyes or lakes, flavors, and sweetening agents may also be present. Diluents are added where the quantity of active ingredient is small or difficult to compress. Common tablet fillers include lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose. Chewable tablets often contain sucrose, mannitol, or sorbitol as fillers. Where the amount of active ingredient is small, the overall tableting properties are in large measure determined by the filler. Because of problems encountered with bioavailability of hydrophobic drugs of low water-solubility, water­soluble diluents are used as fillers for these tablets.

Binders give adhesiveness to the powder during the preliminary granulation and to the compressed tablet. They add to the cohesive strength already available in the diluent. While binders may be added dry, they are more effective when added out of solution. Common binders include acacia, gelatin, sucrose, povidone, methylcellulose, carboxymethylcellulose, and hydrolyzed starch pastes. The most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression.

A disintegrating agent serves to assist in the fragmentation of the tablet after administration. The most widely used tablet disintegrating agent is starch. Chemically modified starches and cellulose, alginic acid, microcrystalline cellulose, and cross-linked povidone, are also used for this purpose. Effervescent mixtures are used in soluble tablet systems as disintegrating agents. The concentration of the disintegrating agent, method of addition, and degree of compaction play a role in effectiveness.

Lubricants reduce friction during the compression and ejection cycle. In addition, they aid in preventing adherence of tablet material to the dies and punches. Metallic stearates, stearic acid, hydrogenated vegetable oils, and talc can be used as lubricants. Because of the nature of this function, most lubricants are hydrophobic, and as such tend to reduce the rates of tablet disintegration and dissolution. Consequently, excessive concentrations of lubricant should be avoided. Polyethylene glycols and some lauryl sulfate salts have been used as soluble lubricants, but such agents generally do not possess optimal lubricating properties, and comparatively high concentrations are usually required.

Glidants are agents that improve powder fluidity, and they are commonly employed in direct compression where no granulation step is involved. The most effective glidants are the colloidal pyrogenic silicas.

Manufacturing Methods

Chewable tablets are prepared by three general methods: Wet granulation, dry granulation (roll compaction or slugging), and direct compression. The purpose of both wet and dry granulation is to improve flow of the mixture and/or to enhance its compressibility.

Dry granulation (slugging) involves the compaction of powders at high pressures into large, often poorly formed tablet compacts. These compacts are then milled and screened to form a granulation of the desired particle size. The advantage of dry granulation is the elimination of both heat and moisture in the processing. Dry granulations can be produced also by extruding powders between hydraulically operated rollers to produce thin cakes which are subsequently screened or milled to give the desired granule size.

Excipients are available that allow production of tablets at high speeds without prior granulation steps. These directly compressible excipients consist of special physical forms of substances such as lactose, sucrose, dextrose, or cellulose, which possess the desirable properties of fluidity and compressibility. The most widely used direct-compaction fillers are microcrystalline cellulose, anhydrous lactose, spray-dried lactose, compressible sucrose, and some forms of modified starches. Direct compression avoids many of the problems associated with wet and dry granulations. However, the inherent physical properties of the individual filler materials are highly critical, and minor variations can alter flow and compression characteristics so as to make them unsuitable for direct compression. The present formulation is presented as chewable tablets. Each tablet contains the active substance Ferric Hydroxide Polymaltose Complex in strength of 100 mg Iron 3+ and weighs 730 mg.

Manufacturing process for chewable tablets should meet the requirements of Good Manufacturing Practice (GMP).

Throughout manufacturing certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production, so the validation of the manufacturing process and the in-process controls are documented.

1. ***P.2.2.2 Product Formula***

All tests during the Formulation Development were performed on Uni-Pharma's three development batches (LAB-01, LAB-02 and LAB-03).

The qualitative and quantitative formula of the finished product is presented in the following table:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **No** | **Name of Ingredient** | **Reference Standards** | **Quantity** | **Units** |
| **Active Substance** | | | | |
| 1. | Ferric Hydroxide  Polymaltose Complex | I.H.S. | 357.000[[1]](#footnote-1) | mg |
| Corresponds to Iron+++ | 100.000\* | mg |
| **Excipients** | | | | |
| 1. | Sodium Cyclamate | Eur. Phar. | 9.000 | mg |
| 2. | Vanillin | Eur. Phar. | 2.900 | mg |
| 3. | Macrogol 6000 | Eur. Phar. | 37.000 | mg |
| 4. | White Chocolate Flavor | I.H.S. | 0.600 | mg |
| 5. | Dextrates | USP-NF. | 261.000 | mg |
| 6. | Talc (Purified) | Eur. Phar. | 21.000 | mg |
| 7. | Cellulose  Microcrystalline | Eur. Phar. | q.s. 730.000  (41.500) | mg |
| 8. | Water Purified**[[2]](#footnote-2)** | Eur. Phar. | - | - |

Where I.H.S: In-House Specifications.

*Y* ( *Kg* )

n

• 100

n: % Content of Ferric Hydroxide Polymaltose Complex in *Fe*

X: Quantity to be weighed.

**\*\***Solvent that is evaporated during production.

1. ***P.2.2.3 Overages***

Not applicable.

1. ***P.2.2.4 Physicochemical and Biological Properties***

*Physicochemical properties (Active substance):*

Physical Description

*Ferric Hydroxide Polymaltose Complex* is a brown or dark brown, odorless powder.

Solubility

The complex is water soluble and insoluble in ordinary organic solvents.

Polymorphism

Since *Ferric Hydroxide Polymaltose Complex* is an amorphous powder, polymorphism phenomena take no place.

pH

The pH value of a 5% w/v aqueous solution of Iron (III) is between 5.5 and 7.5.

Please also refer to section *3.2.S.1.3*.

*Physicochemical properties (drug product):*

In this section the physicochemical parameters relevant to the performance of the drug product are discussed. Taking into consideration the pharmaceutical form of the medicinal product, the physicochemical properties that should be addressed are the appearance of the tablet, the identification and quantitative determination of the drug substances, the uniformity of mass, the uniformity of dosage units (mass variation), resistance to crushing, friability, disintegration, as well as the product's microbiological quality.

All the specifications were also met during the stability studies. Please refer to section *3.2.P.8.3*.

1. ***P.2.3 Manufacturing Process Development***

The manufacturing process development took place on three lab-scale batches (LAB-01, LAB-02 and LAB-03), in order to study the development of the most suitable manufacturing process that will provide a product with the desired characteristics and an ‘easy-to-handle' manufacturing process.

On the manufacturing process diagram shown in section 3.2.P.2, representing the manufacturing process of LAB-01, a solution of PEG 6000 is prepared by diluting a part of the excipient in warm, purified water (Stage A), which is later on added into the appropriate quantity of the weighed active substance Ferric Hydroxide Polymaltose Complex (Stage B). A kneading procedure follows and the mixture is later on dried and sieved to obtain a fine granule.

A second solution with the rest of the amount of PEG 6000 is prepared in warm, purified water (Stage C), where a mixture of pre-sieved Vanillin, the flavoring agent, Dextrates and the sweetener, Sodium Cyclamate, are later on added into the PEG 6000 solution. A kneading procedure follows and the mixture is later on dried and sieved, in order to obtain a fine granule (Stage D).

The two dried and pre-sieved mixtures are then mixed together (Stage E) with simultaneous addition Microcrystalline Cellulose and Talc (Stage F). Mixing, weighing and tabletting of the resulting granule are the final steps of the manufacturing process.

On the second manufacturing process diagram shown in section 3.2.P.2, representing the manufacturing process of batch encoded as LAB-02, the same procedure was kept as in the manufacturing process of LAB-01, with the only difference being the stage and the form where PEG 6000 will be added.

PEG 6000 used was again splitted in two parts. The first part was added into the active substance's kneading solution (Stage A) while the second was later on added into the final mixture in solid form (Stages E & F), actually replacing the Dextrates solid form addition in the final mixing (Stage F).

On the third manufacturing process diagram shown in section 3.2.P.2, representing the manufacturing process of batch encoded as LAB-03, the same procedure was kept as in the manufacturing process of LAB-02, with the difference that the rest of the amount of PEG 6000 that was left aside after the kneading procedure (Stage A), is now kneaded together along with a part of Dextrates (Stages C & D).

The other part of Dextrates is added later on to the final granule mixing (Stage E) in solid form, in order to improve the granule's tableting properties.

The batch encoded as LAB-01 presented very strong binding properties, since the whole amount of Dextrates along with a part of PEG 6000 were dissolved in water. This resulted in obtaining tablets with big values in resistance to crushing (over 9 kp) as well as extremely slow disintegration, since both excipients acted strongly as binders.

More specifically, the resulting mixture (Stage E) was very hard to handle along production, while stickiness occurred in the kneading machinery and the drum mixers. In addition, mixing, as well as sieving of the granule (deriving from mixing of Stages C & D) at the end, was also an issue.

For all the above obstacles and the disadvantages in the resulting final product, this manufacturing process was rejected.

The batch encoded as LAB-02 presented the opposite actions than LAB-01. Since a part of PEG 6000 was decided to be added directly as a powder on Stage F and not to participate in the kneading procedure as on Stage D of LAB-01, leaving only Dextrates to act as a binder this time, the lubrication of the final mixture was extreme. That leaded to bad dispersion of the two granule mixes in Stage E, which later resulted in bad uniformity of the tablets. Tableting procedure became also an issue, since the free flowing PEG 6000 powder in the final granule mix acted strongly as an antiadherent.

For all the above obstacles, this manufacturing process was also rejected.

The idea then, while proceeding to the manufacturing process of a batch encoded as LAB- 03, was to combine in the second kneading procedure (Stage D) a part of PEG 6000 along with a part of Dextrates, in order to succeed a satisfying binding while tableting.

The effect of over-lubrication observed in LAB-02 was expected to be avoided this time, by choosing to use PEG 6000 solely as a binder and leaving a part of Dextrates to be added in solid form later on the final granule mixing (Stage E).

This variation was also expected to improve the tableting properties, leaving Dextrates to act solely as a directly compressible tablet diluent, while the lubrication of the granule would be improved only by the use of purified Talc.

***Conclusions***

The batch encoded as LAB-03 presented good behaviour while kneading, mixing and sieving of all granule intermediates, as well as in the rest manufacturing stages.

The final mixing granule of Stages E & F presented good blending uniformity, while the resulting lubrication during tableting was proved to be satisfactory, only with the use of Purified Talc.

The tablets produced had acceptable resistance to crushing values, disintegration time and uniformity in Fe3+, proving the suitability of the chosen kneading processes and the certain excipient's binding properties when used this way.

For all the above mentioned advantages, *the manufacturing process applied for the production of batch LAB-03 is selected as the official manufacturing process,* also described in *3.2.P.3.3.*

Three more lab-scales batches, LAB-04, LAB-05 and LAB-06 were manufactured right after the manufacturing process development trials, using the *official manufacturing process* mentioned above. Samples from LAB-04, LAB-05 and LAB-06 were used for supporting the first, indicative dissolution profile tests that were performed, as well as the rest of the physicochemical tests, in order to ensure that the final product meets the specifications set and described in *§3.2.P.2.3.5.*

For a detailed validation and evaluation of the *official manufacturing process,* please refer to section *3.2.P.3.5.*

1. ***P.2.3.1 Critical steps***

The following steps of the manufacturing process chosen should be considered as critical:

* The blending Stage F is considered essential in order to produce a blend, where the active ingredient has been uniformly distributed.
* Tableting is considered essential for uniformity of tablets' mass and for tablets' disintegration characteristics, as well as for the tablets' resistance to crushing and friability.

For a detailed description and the equipment used in the manufacturing process of **Ferric Hydroxide Polymaltose Complex/UNI-PHARMA *Chw. tablets 100 mg/tab***, please refer to section *3.2.P.3*.

The manufacturing process should be well-controlled and in-process testing must be adequate to ensure consistent quality in the product. The manufacturing process for solid preparations for oral use, should meet the requirements of Good Manufacturing Practice (GMP).

In the manufacture of solid preparations for oral use, measures are taken to:

* Ensure that all ingredients are of appropriate quality
* Minimize the risk of microbial contamination
* Minimize the risk of cross-contamination

Appropriate measures should also be taken to optimize the stability of the active ingredient(s). Additional measures should be taken so that, when stored under the conditions stated on the label, the product is not subject to any kind of deterioration.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production.

The validation of the *official manufacturing process* and the in-process controls are documented. Please refer to sections *3.2.P.3.5* and *3.2.P.3.3.5* respectively.

1. ***P.2.3.2 Control of Starting Materials, Excipients and Active Substance(s)***

A detailed specification listing including all required tests according to the current relative Pharmacopoeia -or I.H.S where applicable- for both the active substances and excipients used in the formula is essential.

Please refer to section *3.2.S.4.1 Specifications of drug substances* for the active substance and to section *3.2.P.4 Control of Excipients* for all the excipients used in the current formula.

1. ***P.2.3.3 Environmental conditions***

The prerequisite for controlled environment is due to the nature of the raw materials used for its production. Standard relative humidity and moderate to cool temperatures in the manufacturing areas according to GMP are essential to prevent the granulations or tablets from sticking to the machinery and from picking up extra moisture from the air, which may cause product degradation after wet granulation procedure. The whole process is generally carried out in a completely closed and integrated handling system, consisting of intermediate bulk containers (IBCs), tumblers for IBCs, docking and dosing stations. Complete drying of all the equipment after a cleaning process is essential to prevent erratic granulation. All these equipment must also allow proper venting of air, with tolerable moisture levels.

This method of manufacturing is summarized as open handling of the product, which allows the use of much simpler types of equipment, but manufacturing area must have maximum tolerable moisture levels and moderate to cool temperatures.

1. ***P.2.3.4 Selected manufacturing process***

The flowchart presented in the relevant section in Module 3 shows the proposed manufacturing process of **Ferric Hydroxide Polymaltose Complex/UNI-PHARMA *Chw. tablets 100 mg/tab.***

1. ***P.2.3.5 Control of Finished Product***

The finished product consists of a chewable tablet having 357 mg (equivalent to 100 mg Fe3+) strength per tablet in Ferric Hydroxide Polymaltose Complex. Each chewable tablet weighs 730.0 mg.

***Specifications of the finished product***

|  |  |  |
| --- | --- | --- |
| **Appearance-Description** | Brown/White, mosaic, cylindrical tablets of 12.0 ± 2 mm diameter | |
| **Identification of Iron+++** | Positive to Iron+++ | by Color Reaction |
| **Quantitative determination** | Iron+++ is determined using complexometric titration | |
| **of the Active Substances** | 95 - 105 % Iron+++ of the stated amount during batch release and shelf life | |
| **Related Substances: Free Iron (III)** | NMT 0.05% of drug substance (ferric hydroxide polymaltose) | |
| **Average weight** | 730 mg ± 5.0 % at the time of batch release and during the shelf life of the product | |
| **Uniformity of Dosage units**  **Eur. Ph. *2.9.40*** | Iron+++: Mass variation test, AV < L1 (L1 = 15) at the time of batch release | |
| **Resistance to crushing Eur. Ph. *2.9.5*** | 5 - 9 kp at the time of batch release and 4-9 kp during the shelf life of the product | |
| **Friability Eur. Ph. *2.9.7.*** | Not more than 1 % w/w | |
| **Disintegration Eur. Ph. *2.9.1*** | Not greater than 30 min, measured as described in the current Eur. Ph., using H2O as the disintegration medium | |
| **Microbial Quality According to Eur. Ph. *5.1.4* Table 1** | | |
| **Total Aerobic Microbial Count *(TAMC 2.6.12)*** | | Not more than 103 bacteria per gram |
| **Total Yeast Microbial Count *(TYMC 2.6.12)*** | | Not more than 102 per gram |
| **E. Coli *(2.6.13):*** | | Absence, per gram |

All control methods are fully described in the current Eur. Pharm.

Relevant test methods have been validated according to ICH requirements.

1. ***P.2.4 Container Closure System***

Based on the results of stability study the product is considered stable when stored in transparent ALU/ALU blisters. The blisters are subsequently packed into cardboard boxes. Results from tests regarding container closure impermeability/self sealability were found to be acceptable.

1. ***P.2.4.1 Container (brief description)***

The container type and materials used are of excellent quality and according to the required standards of the Pharmacopoeia. They also provide the required protection and stability of the product during its storage and transportation.

The primary container is ALU/ALU blister. The stability trials on the final product were carried out with this type of primary packaging and showed that the tablets are stable for 6 months at 40°C/75% RH. For a detailed description of the container please refer to section

* 1. *P.7*.

1. ***P.2.4.2 Type of packaging material***

Every 10 chewable tablets are enclosed into ALU/ALU blisters so that the product is shielded from the environmental conditions, especially from humidity. Each outer carton box container encloses 3 ALU/ALU blisters with 10 tablets each (3 blisters x 10 tablets) along with a Patient Information Leaflet. For a detailed description please refer to section

* 1. *P.7*.

1. ***P.2.4.3 Quality specifications (routine tests)***

The packaging materials are checked on a regular basis for the following qualities:

Test for physical dimensions

* Width (mm)
* Weight (g/cm2)

Satisfactory specifications for the container and closure components have been provided. The packaging materials have been subjected to rigorous integrity testing and have been found to be satisfactory.

All primary product packaging complies with EU legislation regarding contact with food.

1. ***P.2.5 Microbiological Attributes***

The microbiological quality of the product according to the following tests is not routinely performed. Microbiological testing is performed on at least one batch per year or every 10th batch whichever is the most frequent.

The pharmaceutical preparations should comply with the criteria given below for § 5.1.4. Table 1:

Limits of acceptance:

|  |  |
| --- | --- |
| **Total Aerobic Microbial Count**  ***(TAMC, Eur. Ph. 2.6.12.)*** | Not more than 103 bacteria per gram |
| **Total Combined Yeasts/Moulds Count**  ***(TYMC, Eur. Ph. 2.6.12)*** | Not more than 102 per gram |
| **E. coli *(Eur. Ph. 2.6.13.)*** | Absent |

The control includes the determination of total aerobic living micro-organisms that is located in the final product. It is executed according to the specifications and directives of current European Pharmacopoeia (§ 5.1.4. Table 1).

1. ***P.2.6 Compatibility***

Not applicable.

**CONCLUSIONS**

The Chewable tablets composition consists of Ferric hydroxide Polymaltose Complex, which corresponds to 100 mg of Iron3+ and is administered as it is, without further dilution. The product is packed in ALU/ALU blisters.

Full information is provided in the dossier to justify the quality of batches. Excipients used in the manufacture of the product are considered safe and common for use in such kind of preparations. The dossier provides a suitable description of the active substance and the chosen formulation and confirms production of the active substance and of the final product at a consistent quality. Analytical methods are well described and data of their validation confirm their suitability.

Manufacturing processes are sufficiently detailed for all preparations and demonstrate that production of the final product is subject to a consistent quality. The specifications for the final product contain sufficient acceptance criteria and corresponding tests. Stability studies have been performed according to ICH guidelines.

The stability studies on the finished product justify a shelf-life of 36 months at 30 °C ± 2 °C / 65% RH ± 5%.

1. ***P.3 MANUFACTURE***
2. ***P.3.1 Manufacture(s)***

Manufacturers of the finished dosage form:

UNI-PHARMA KLEON TSETIS PHARMACEUTICAL LABORATORIES S.A.

14th km National Road 1,

GR-145 64, Kifissia, Greece

UNI-PHARMA KLEON TSETIS, PHARMACEUTICAL LABORATORIES S.A., possesses:

* “Manufacturing Licence”
* “Good Manufacturing Practice Certificate”

from the Greek National Organization for Medicines.

1. ***P.3.2 Batch Formula***

Product:

**Ferric Hydroxide Polymaltose Complex/UNI-PHARMA *Chw. tablets 100 mg/tab***

* *Size of a full-scale batch:* 400,000 tablets or 292.0 kg or 13,333BT x 30 tabs x 730.0 mg
* *Composition of a full-scale batch:*

|  |  |  |
| --- | --- | --- |
|  | **Composition per tablet**  **(mg)** | **Composition per batch**  **(kg)** |
| ***Active ingredient(s):*** |  |  |
| Ferric Hydroxide Polymaltose  Complex | 357.001  (Equivalent to 100.00 mg *Iron+++*) | A2 |
| ***Non active ingredients:*** |  |  |
| Sodium Cyclamate | 9.00 | 3.60 |
| Vanillin | 2.90 | 1.16 |
| Talc | 21.00 | 8.40 |
| Polyethylene Glycol 6000  (Macrogol 6000) | 37.00 | 14.80 |
| Chocolate Flavor | 0.60 | 0.24 |
| Dextrates (Emdex) | 261.00 | 104.40 |
| Cellulose Microcrystalline | Q.S. 730.00 | B[[3]](#footnote-3) |
| Water Purified[[4]](#footnote-4) | - | 26.00 |

1Theoretical value. The accurate value is calculated each time taking into account the % assay of iron in the drug substance.

2The purity and the moisture in the drug substance should be taken into account. The weighted amount of iron polymaltose should correspond to 40.000 kg Fe+++ and can be calculated according to:

**40.000** *kg* **X 100**

*A =*

n

Where,

n: %Assay of Fe+++

A: The weighted amount (kg)

4Solvent that is evaporated during production.

1. ***P.3.3 Manufacturing procedure***

A brief description of the manufacturing process of the tablet is presented underneath.

1. Drug substance granulation

Stage A.1: Granulation liquid preparation

Inside the portable stirrer PEG 6000 melts in 60-70°C. After, hot purified water is added and the whole mixture is homogenized at the indication “30”.

Stage A.2: Granulation of active ingredient

Ferric Hydroxide Polymaltose Complex is added in the mixer and is kneaded together with the solution from the previous stage. The mixture is being mixed at 70 rpm for 150 minutes.

Stage A.3: Drying of active ingredient granules

The granulated mass is put in an oven at 40°C, where it is dried until the moisture content is < 5.0% KF.

Stage A.4: Sizing and weighing of dry granules

The dried granules are passed through a 20-mesh sieve. The sieved granules are then stored inside barrels and are weighted.

1. Granulation of essences

Stage B.1: Sizing and mixing of essences

Part of the Dextrates quantity, Chocolate Flavour, Sodium Cyclamate and Vanillin are sieved through a 20-mesh sieve and are mixed using the mixer for 20 min at 15 rpm.

Stage B.2: Granulation liquid preparation

The granulation solution is prepared by melting PEG 6000 at 60-70°C inside the portable stirrer and is mixed with hot purified water at the indication “30”.

Stage B.3: Granulation of essences

The mixture of the first step is kneaded at the mixer, together with the aforementioned solution, at 15 rpm until the creation of a satisfying granule. If necessary, more Purified water is added.

Stage B.4: Drying of essences granules

The kneaded mass is put in the oven for drying, in room temperature about 25°C, until the moisture content is < 5.0% (KF).

Stage B.5: Sizing and weighing of dry granules

The dried granules are passed through a 20-mesh sieve. The sieved granules are then stored inside barrels and are weighted.

1. Final Blending

Stage C.1: Blending of granules and excipients

In the mixer the granulated Ferrum and the granulated essences are added and mixed at 100 rpm, for 30 min along with the excipients Dextrates, Microcrystalline cellulose 101 and Talc after being sieved through a 20-mesh sieve.

Stage C.2: Weighing of bulk blend

The mixture of stage C.1 is stored inside barrels and weighted.

1. Tableting

Stage D.1: Tableting

The final mixture is transferred to the tableting room and is compressed into tablets with the following specifications:

Average weight: 730 mg

Minimum weight: 694 mg

Maximum weight: 766 mg Resistance to crushing: 5.0 - 9.0 kp

Diameter: 12 mm

Disintegration time: < 30min

Water content: < 5.0 KF

Before the tableting procedure, the punches are controlled and rotated according to F

08.04.11.02.

Stage D.2: Weighing of bulk tablets

The tablets are weighted, and the process step yield is calculated.

1. Packaging

The tablets are packed into ALU/ALU blisters of 10 tablets each. The blisters are further packed in boxes along with the Patient Information Leaflet.

***3.2.P.3.3.4 Critical steps***

The following steps of the manufacturing process should be considered as critical:

Stage C.1:

The final blending of stage C.1 is considered essential in order to produce a blend, where the active ingredient has been uniformly distributed.

Stage D.1:

Tableting is considered essential for the uniformity of tablets' mass, and for tablets' disintegration characteristics, as well as resistance to crushing and friability.

1. ***P.3.4 Process Validation and/or Evaluation***

Validation strategy

The purpose of this protocol is to develop a Process Validation protocol for Manufacturing of **Ferric Hydroxide Polymaltose Complex/Uni-Pharma Chew. tablets 100 mg/tab** in the new manufacturing line.

Furthermore, the protocol establishes documentary evidence that provides an assurance that the critical process variables are under control.

Finally, the protocol demonstrates that the entire of manufacturing, filtration, filling and sterilization shall consistently produce the product, meeting approved regulatory specifications and quality attributes.

For the validation three batches of the product **Ferric Hydroxide Polymaltose Complex/Uni-Pharma Chew. tablets 100 mg/tab** ags are used, namely:

• ***22-008***

* ***22-009***
* ***22-010***

These batches were produced as follows:

***Table 3.2.P.3.5.1: Batches identity***

|  |  |  |  |
| --- | --- | --- | --- |
| **Content** | **Batch number** | **Manufacturing date** | **Batch size (tablets)** |
| **100 mg/tab** | *22-008* | *04/2022* | *400,000* |
| *22-009* | *04/2022* | *400,000* |
| *22-010* | *05/2022* | *400,000* |

Please refer to Module 3 for the validation of manufacturing procedure.

1. ***P.4 CONTROL OF EXCIPIENTS***

All excipients contained in the Drug Product have a Pharmacopoeial status and specifications have been worked out in line with current Ph. Eur. Monographs.

**EXCIPIENTS DESCRIBED IN A PHARMACOPOEIA:**

|  |  |
| --- | --- |
| Sodium Cyclamate | Current Eur. Pharm. |
| Vanillin | Current Eur. Pharm |
| Polyethylene Glycol 6000 | Current Eur. Pharm |
| Dextrates | Current USP |
| Cellulose Microcrystalline | Current Eur. Pharm |
| Talc Purified | Current Eur. Pharm |

**EXCIPIENTS NOT DESCRIBED IN A PHARMACOPOEIA**

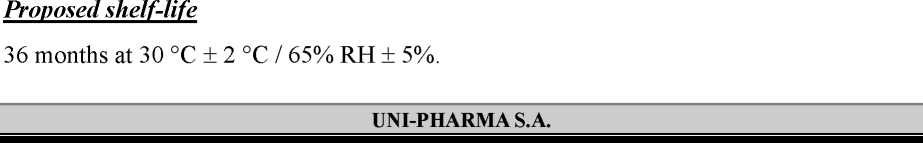
|  |  |
| --- | --- |
| White Chocolate Flavor | I.H.S / Manufacturer |

All suppliers of the excipients are interchangeable as long as the excipients meet the finished product manufacturer's specifications. The Certificates of Analysis of some indicative suppliers can be found in the following pages.

All tests are routinely performed on receipt of excipient at the site of product manufacture.

1. ***P.5 CONTROL OF DRUG PRODUCT***
2. ***P.5.1 Specification(s)***

|  |  |  |
| --- | --- | --- |
| **Appearance-Description** | Brown/White, control | mosaic, cylindrical tablets of 12.0 ± 2.0 mm diameter. Visua |
| **Identification of Iron+++** | Positive to Iron+++ by Color Reaction. | |
| **Quantitative determination** | Iron+++ is determined using complexometric titration | |
| **of the Active Substances** | 95% - 105% Iron+++ of the stated amount during batch release and shelf life | |
| **Related Substances: Free Iron (III)** | NMT 0.05% of drug substance (ferric hydroxide polymaltose) | |
| **Average weight** | 730 mg ± 5.0 % at the time of batch release and during the shelf life of the product | |
| **Uniformity of Dosage units**  **Eur. Ph. *§2.9.40*** | Iron+++: Mass variation test, AV < L1 (L1 = 15.0) at the time of batch releas | |
| **Resistance to crushing Eur. Ph. *§2.9.5*** | 5 - 9 kp at the time of batch release and 4 - 9 kp during the shelf life of the product | |
| **Friability Eur. Ph. *§2.9.7.*** | Not more than 1% w/w | |
| **Disintegration Eur. Ph. *§2.9.1*** | Not greater than 30 min, measured as described in the current Eur. Ph., usin H2O as the disintegration medium | |
| **Microbial Quality According to Eur. Ph. *5.1.4* Table 1** | | |
| **Total Aerobic Microbial Count *(TAMC §2.6.12)*** | | Not more than 103 bacteria per gram |
| **Total Yeast Microbial Count *(TYMC §2.6.12)*** | | Not more than 102 per gram |
| **E. Coli *(§2.6.13):*** | | Absence, per gram |



1. ***P.5.2 Batch analyses***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **BATCH** | **Manufacturing Date** | **Manufacturing Plant** | **Batch Size** | **Purpose of Production** |
| 14-01 | 02/2014 |  | 400,000 tabs |  |
| 14-02 | 02/2014 | **UNI-PHARMA KLEON TSETIS PHARMACEUTICAL LABORATORIES S.A.** | 400,000 tabs | Stability studies |
| 15-01 | 06/2015 |  | 400,000 tabs |  |

1. ***P.6 REFERENCE STANDARDS OR MATERIALS***

Iron3+:

*Not applicable since the method is executed via complexometric titration.*

The analytical method for testing the assay of *Ferric Hydroxide Polymaltose Complex* content in the drug product is a titration method (“Complexometric titration”).

For this analytical method (please refer to section *3.2.P.5.2* accordingly), the *Ferric Hydroxide Polymaltose Complex* is assayed by titrating it with a Certified 0.1 M Disodium Edetate solution, until a visible color change of the solution occurs.

For such a titration, there is no need for a reference standard (primary standard, secondary standard, working standard, etc.). *Any approved sample of production grade Ferric Hydroxide Polymaltose Complex drug substance material and a certified titrant solution will suffice to perform this analysis*.

Therefore, there are no drug substance reference standards available.

Please find attached in Module 3 two indicative Certificates of Analysis of the titrant solution.

1. ***P.7 CONTAINER CLOSURE***
2. ***P.7.1 Container (brief description)***

The primary container is ALU/ALU blister. The stability trials on the final product were carried out with this type of primary packaging and showed that the tablets are stable (please refer to section *3.2.P.8.3*).

The secondary packaging is cardboard box containing 3 blister strips each of 10 tablets, to give a pack size of 30 chewable tablets, along with a Patient Information Leaflet.

1. ***P.7.2 Type of packaging material and composition***

Blister Bottom Laminate, Cold Form (ALU-ALU), is consisted out of OPA film of 25 microns/Aluminium Soft Foil 45 microns/PVC film 60 microns. The Aluminium ‘dull' side is laminated to OPA film, while the ‘bright' side is laminated to PVC Film.

Every 10 chewable tablets are enclosed into ALU-ALU blisters so that the product is shielded from the environmental conditions, especially from humidity.

1. ***P.7.3 Quality specifications (routine tests)***

The packaging materials are checked on a regular basis for the following qualities:

Test for physical dimensions:

* Width (mm)
* Weight (g/cm2)

Satisfactory specifications for the container and closure components have been provided. The packaging materials have been subjected to rigorous integrity testing and have been found to be satisfactory.

All primary product packaging complies with EU legislation regarding contact with food.

1. ***P.8 STABILITY***

The regular stability program of **Ferric Hydroxide Polymaltose Complex / UNI­PHARMA *Chw. tablets 100 mg/tab*** started in February 2014.

1. ***P.8.1.2 Scope***

The scope of the performed stability studies is to provide evidence, based on the stability data, for defining the proposed shelf-life of the product. The results from the stability studies are summarized and evaluated hereunder.

*Table 3.2.P.8.1.1* Stability batches

|  |  |  |
| --- | --- | --- |
| **Batch number** | **Manufacturing Date** | **Batch size** |
| 14-01 | 02/2014 | 400,000 tabs |
| 14-02 | 02/2014 | 400,000 tabs |
| 15-01 | 06/2015 | 400,000 tabs |

1. ***P.8.1.3 Stability Tests on the Active Ingredient***

Please refer to section *3.2.S.7* of the ASMF of the manufacturers.

1. ***P.8.1.4 Stability Tests on the Finished Product***

Stability summary

1. Suggested shelf-life
2. Methodology
3. Analytical tests
4. Shelf-life specifications
5. Discussion - Conclusion
6. ***Suggested shelf-life***

36 months.

1. ***Methodology***

***2.1 Real-time studies (physical stability) / long term stability studies***

*Table 2.3.P.8.1.2* Stability batches - long term stability studies

|  |  |  |
| --- | --- | --- |
| **Batch number** | **Manufacturing Date** | **Batch size** |
| 14-01 | 02/2014 | 400,000 tabs |
| 14-02 | 02/2014 | 400,000 tabs |
| 15-01 | 06/2015 | 400,000 tabs |

Storage conditions

Controlled room temperature and humidity (30 °C ± 2 °C / 65% RH ± 5%).

Container Closure System

Every 10 chewable tablets are enclosed into ALU/ALU blisters so that the product is shielded from the environmental conditions, especially from humidity. Each outer box container encloses 3 blisters with 10 tablets each (Blister 3x10) and a Patient Information Leaflet.

* 1. ***Accelerated conditions stability studies***

*Table 2.3.P.8.1.3* Stability batches - accelerated stability studies

|  |  |  |
| --- | --- | --- |
| **Batch number** | **Manufacturing Date** | **Batch size** |
| 14-01 | 02/2014 | 400,000 tabs |
| 14-02 | 02/2014 | 400,000 tabs |
| 15-01 | 06/2015 | 400,000 tabs |

Storage conditions

Controlled room temperature and humidity (40 °C ± 2 °C / 75% RH ± 5%).

Container Closure System

Every 10 chewable tablets are enclosed into ALU/ALU blisters so that the product is shielded from the environmental conditions, especially from humidity. Each outer box container encloses 3 ALU/ALU blisters with 10 tablets each (Blister 3x10) and a Patient Information Leaflet.

1. ***Analytical tests***

*Table 3.2.P.8.1.4* Stability protocol

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **CONDITIONS** | **TESTING INTERVALS (in months)** | | | | | | |
| **3** | **6** | **9** | **12** | **18** | **24** | **36** |
| **Long-term**  **30°C ± 2°C / 65% RH ± 5%** | X | X | X | X | X | X | X |
| **Accelerated**  **40°C ± 2°C / 75% RH ± 5%** | X | X |  |  |  |  |  |

***3.1 Appearance -Physical stability***

- Appearance

- Disintegration time

- Average weight

- Resistance to crushing

* 1. ***Chemical stability***

- Identification of Iron+++

- % Assay of Iron+++

- Free Iron+++

* 1. ***Biological stability***

The methodology of the tests is described in details in the corresponding paragraphs of this document (please refer to paragraph *3.2.P.5.2.5*).

The control includes the determination of total aerobic living micro-organisms located in the final product. It is executed according to the specifications and directives of current European Pharmacopoeia *(§ 5.1.4. Table 1)*.

For the description of the analytical methods used please refer to section *3.2.P.5.2*.

1. ***Shelf life specifications***

|  |  |  |
| --- | --- | --- |
| **Appearance-Description** | Brown/White, mosaic, cylindrical tablets of 12.0 ± 2.0 mm diameter. Visual control | |
| **Identification of Iron+++** | Positive to Iron+++ by Color Reaction. | |
| **Quantitative determination of the Active Substances** | Iron+++ is determined using complexometric titration  95% - 105% Iron+++ of the stated amount during batch release and shelf life | |
| **Related Substances: Free Iron (III)** | NMT 0.05% of drug substance (ferric hydroxide polymaltose) | |
| **Average weight** | 730 mg ± 5.0 % at the time of batch release and during the shelf life of the product | |
| **Uniformity of Dosage units**  **Eur. Ph. *§2.9.40*** | Iron+++: Mass variation test, AV < L1 (L1 = 15.0) at the time of batch release | |
| **Resistance to crushing Eur. Ph. *§2.9.5*** | 5 - 9 kp at the time of batch release and 4 - 9 kp during the shelf life of the product | |
| **Friability Eur. Ph. *§2.9.7.*** | Not more than 1% w/w | |
| **Disintegration Eur. Ph. *§2.9.1*** | Not greater than 30 min, measured as described in the current Eur. Ph., using H2O as the disintegration medium | |
| **Microbial Quality According to Eur. Ph. *5.1.4* Table 1** | | |
| **Total Aerobic Microbial Count *(TAMC §2.6.12)*** | | Not more than 103 bacteria per gram |
| **Total Yeast Microbial Count *(TYMC §2.6.12)*** | | Not more than 102 per gram |
| **E. Coli *(§2.6.13):*** | | Absence, per gram |

1. ***Discussion - Conclusion***

The up to date stability results (Long-term stability and Accelerated stability), during the shelf life of the product, show that **Ferric Hydroxide Polymaltose Complex / UNI­PHARMA *Chw. tablets 100 mg/tab*** fully complies with the defined specifications in all parameters considered.

Finished product stability studies have been conducted in accordance with current guidelines.

Based on the results, a shelf-life of 36 months has been set, which is satisfactory.

Proposed shelf life:

36 months at 30 °C ± 2 °C / 65% RH ± 5%

1. ***P.8.2 Post-Approval Stability Protocol and Stability Commitment***

The proposed production batch size of **Ferric Hydroxide Polymaltose Complex / UNI­PHARMA *Chw. tablets 100 mg/tab*** is 400,000 tablets.

A stability study will be undertaken on the first three commercial batches, under long-term conditions (30 oC ± 2 oC /65% ± 5% RH for 36 months) and accelerated conditions (40 oC ± 2 oC / 75% ± 5% RH for 6 months), according to the following protocol:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **CONDITIONS** | **TESTING INTERVALS (in months)** | | | | | | |
| **3** | **6** | **9** | **12** | **18** | **24** | **36** |
| **Long-term**  **30OC ± 2OC / 65% RH ± 5%** | X | X | X | X | X | X | X |
| **Accelerated**  **40OC ± 2OC / 75% RH ± 5%** | X | X |  |  |  |  |  |

The up-to-date stability results (Long-term stability, Intermediate and Accelerated stability) are discussed under sections *3.2.P.8.1 Stability Summary and Conclusion* and *3*.*2.P.8.3 Stability Data*.

1. ***P.8.3 Stability Data***

For the stability data please refer to the tables presented in section 3.2.P.8.3.

Conclusion

The up-to-date stability results (36 months at 30oC/ 65% RH and 6 months at 40oC/ 75% RH), during the shelf life of the product, show that **Ferric Hydroxide Polymaltose Complex / UNI-PHARMA *Chw. tablets 100 mg/tab*** fully complies with the defined specifications in all parameters considered.

***Proposed shelf-life***

36 months at 30 °C ± 2 °C / 65% RH ± 5%.

1. A APPENDICES
2. ***A.1 Facilities and Equipment***

Facility for the production of solution for infusion.

***A) Manufacturing Equipment***

The following table contains the equipment used for the production of the product

**Paracetamol/Uni-Pharma *Sol. inf. 1 g/100ml***.

*Table 2.3.A.1.1:*

*Equipment used for the production of the injectable solution*

|  |
| --- |
| **EQUIPMENT** |
| • Water distiller |
| • Stainless steel vessel with stirrer for the preparation of the solution for infusion |
| • Stainless steel vessel for the filtrate |
| • Nitrogen gas apparatus |
| • pH-meter |
| • Filtration apparatus |
| • Filter integrity test apparatus |
| • Bags filling-sealing machine |
| • Vacuum unit |
| • Visual inspection apparatus |
| • Bags overwrapping machine |
| • Steam sterilization autoclave |

The operation of equipment is being validated annually.

***B) Analytical Equipment***

* HPLC Apparatus
* UV Apparatus
* pH meter
* Precision Balance
* T.O.C.

1. ***A.2 Adventitious Agents Safety Evaluation***

The pharmaceutical product contains in its formulation pharmaceutical raw materials (active ingredient and excipients) that do not contain or consist of Genetically Modified Organisms (GMO).

Further more all the raw materials used during the development of the product are widely used in Pharmaceutics for a long period of time with a well documented hypotoxicity.

In addition, the manufacturing process followed for the specific pharmacotechnical form does not present any environmental risk given that during the production process all the necessary precautions are taken in accordance to the latest Safety Regulations.

On the basis of the above mentioned considerations, it is possible to affirm that the product is not a vehicle of transmission of agents that would be pathogen for human health.

1. ***A.3 Excipients***

No new excipients, used for the first time in the composition of the product, are included.

The excipients that were chosen and used in the development of the product are widely used in the technology of pharmaceutical formulations. In order to prove their suitability, studies concerning their compatibility with the active substance (stability and analytical studies) were done. These studies concluded that there are no elements of interference or/and inhibition of the active substance by the excipients (analytically or chemically).

1. R REGIONAL INFORMATION

Not applicable.

1. The calculation is done in a way so that the weighed quantity corresponds to Y Kg [↑](#footnote-ref-1)
2. *Fe+++* based on the content of the raw material in *Fe+++*. [↑](#footnote-ref-2)
3. The quantity of Cellulose Microcrystalline is calculated as follows: [↑](#footnote-ref-3)
4. *S =* (292.000 - A - 132,600) kg [↑](#footnote-ref-4)